Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Final Guidance for Industry

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This document supersedes "Guidance on Preclinical and Clinical Data and Labeling for Breast Prostheses" dated October 5, 1999.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket No. 99D-4003. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Ms. Samie Allen at (301) 594-3090 or email sxn@cdrh.fda.gov.

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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

INTRODUCTION

The purpose of this guidance document is to update the information provided in the draft guidance entitled, "Guidance on Preclinical and Clinical Data and Labeling for Breast Prostheses" dated October 5, 1999 based on our additional scientific review and analysis of published studies, review of breast implant applications, and discussions and correspondence between the Plastic and Reconstructive Surgery Devices Branch (PRSB) and breast implant sponsors.

This guidance provides important preclinical, clinical, and labeling information that should be presented in an investigational device exemptions (IDE), a premarket approval (PMA), or a product development protocol (PDP) application. It may also be useful in the preparation of reclassification petitions and master files. The information discussed is relevant to breast implants filled with silicone gel, saline, and alternative filler intended for breast augmentation, breast reconstruction, and revision. However, this guidance does not address tissue expanders, which are unclassified devices for temporary use.

This guidance document serves as a supplement to other FDA publications on IDE, PMA, and PDP applications and should not be construed as a replacement for these documents. For general IDE information, a sponsor should refer to 21 CFR 812 or to the Investigational Device Exemptions Manual, which can be obtained at http://www.fda.gov/cdrh/manual/idemanul.html. For general PMA information, a sponsor should refer to 21 CFR 814 or to the Premarket Approval Manual, which can be obtained at http://www.fda.gov/cdrh/manual/pmamanul.pdf. Any sponsor considering the PDP option should refer to *the Guidance for Industry: Contents of a Product Development Protocol* for specific input regarding PDP applications; this guidance can be obtained at http://www.fda.gov/cdrh/pdp/pdpguide.pdf.

Although use of this document to prepare preclinical and clinical protocols will not ensure IDE, PMA, or PDP approval, following this guidance should reduce unnecessary work by sponsors and should allow for a more efficient review by FDA.

The Least Burdensome Approach - The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to

Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

DEVICE DESCRIPTION / REGULATORY BACKGROUND

There are three types of breast implants, all of which are intended for breast augmentation, breast reconstruction, and/or revision.

Silicone inflatable (saline-filled) breast prosthesis

A silicone inflatable (saline-filled) breast prosthesis has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, that is inflated to the desired size with sterile isotonic saline before or after implantation. Most of these are single lumen devices with a valve that is sealable by the surgeon or self-sealing for the purposes of filling the prosthesis. The implants have a patch that covers the manufacturing port of the prosthesis. There are two types of saline-filled implants. One type is a fixed volume implant, which is filled with the entire volume of saline at implantation. Another type is an adjustable volume implant, which is filled intraoperatively and has the potential for further postoperative adjustment. Saline-filled implants vary in shell surface (i.e., smooth vs. textured), shape, profile, volume, and shell thickness. The sterile saline used as a filler material should conform to United States Pharmacopeia (USP) standards of Normal Physiological Saline (injection grade) which has a concentration of 0.15M and a pH of 7.2-7.4.

In the *FEDERAL REGISTER* of June 24, 1988 (53 FR 23856), FDA issued a final ruling classifying the silicone inflatable (saline-filled) breast prosthesis into Class III (21 CFR 878.3530). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require premarket approval. On January 8, 1993 (58 FR 3436), FDA issued a proposed rule requiring a PMA. On August 19, 1999 (64 FR 45155), FDA required a PMA or PDP for these devices to be filed with the Agency within 90 days.

Silicone gel-filled breast prosthesis

A silicone gel-filled breast prosthesis has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, that is filled with a fixed amount of silicone gel. Each implant has a patch that covers the manufacturing port of the implant. Silicone gel-filled implants may vary in shell surface (i.e., smooth vs. textured), shape, profile, volume, shell thickness, and number of shell lumens. Most silicone gel-filled implants are non-inflatable/non-adjustable and have shells made from a single or double lumen. However, a multi-lumen silicone gel-filled implant may be designed with a valve for intraoperative filling and postoperative volume adjustments with saline or with the a lumen filled with a fixed amount of saline.

In the *FEDERAL REGISTER* of June 24, 1988 (53 FR 23863), FDA issued a final rule classifying the silicone gel-filled breast prosthesis into class III (21 CFR 878.3540). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require premarket approval. On April 10, 1991 (56 FR 14620), FDA required a PMA for these devices be filed with the Agency within 90 days.

Alternative breast prosthesis

Typically, an alternative breast prosthesis has a silicone rubber shell whose filler contains any material other than saline or silicone gel. The filler material may or may not be a gel. However, an alternative breast implant may also have an alternative shell other than that made from silicone rubber. The sponsor should keep in mind that the additional information other than that described below may be necessary for alternative shell breast implants.

All alternative breast prostheses are class III post-amendment devices that require an approved PMA or PDP for marketing.

PRECLINICAL DATA

All preclinical testing (chemical, toxicology, or mechanical) should be performed on the final sterilized product or components thereof. The type of information below should be provided for an IDE, PMA, or PDP unless an adequate rationale is provided.

1. Preclinical Data - Chemistry

1.1 General Information

A complete list of all of the chemicals used in the manufacture of the breast implant should be provided. The list should include the common names and trade names of each chemical component, the specific role of each chemical in the manufacturing process and/or in the final device. The location of the chemical within the device should be provided (e.g., in the shell, the inner or outer layers of the shell, in the filler, valve, or adhesive). A polymeric component should be described by the chemical name, the mean molecular weight, and a measure of the polydispersity. Material safety data sheets (MSDS) should be provided for each chemical. Respective Master Access File (MAF) numbers for all the materials used should be provided.

Changes in design features, such as texturing, variations of device components such as patches or valves, or changes in sterilization may necessitate additional analyses to detect variations in chemical composition.

1.2 Chemical Analysis of Elastomer Shell including Patch and Valve

1.2.1 Extent of Crosslinking

The breast implant shell manufacture involves curing of polymeric components of silicones by chemical crosslinking. The extent of crosslinking should be provided from at least three different lots. One of the following methods may be utilized to determine the degree of crosslinking:

- measurement of Young's modulus at low strain; this is approximately proportional to crosslink density
- measurement of equilibrium swelling of the polymeric component by a good solvent
- determination of the amount of unreacted crosslinker from the total extractables

1.2.2 Extractables

An analysis of the extractable or releasable chemicals of an implant is necessary for the assessment of the safety of the device. The identification and quantification of releasable chemicals should be provided to identify potentially toxic chemicals and estimate the upper limits of the chemicals that could be released to the patient.

The following is one suggested method to address this issue. The extraction of the shell for chemical analysis can be performed with at least one polar solvent (i.e., ethanol or a mixture of ethanol-water) and two non-polar solvents (i.e., dichloromethane and hexane). The extraction experiments should be conducted at 37°C. To determine the duration of the exhaustive extractions, a series of successive extractions can then be conducted by exposing the sample to the solvent for a period of time, analyzing the solvent for extractables, replacing with fresh solvent, again exposing the sample for a period of time, analyzing, and repeating the process. When the level of the analyte for the extraction is one-tenth (0.1) the level in the previous extraction, the extraction is deemed complete so that a 10% correction to the total extractable material can be applied. In cases where this condition may not occur because of extremely slow migration of the higher molecular weight material, the test can be applied to the contents of the extract with molecular weights below 1500 because these are the compounds of greatest interest. All the separate analyte levels are then added together to calculate the cumulative value and, via the sample/solvent ratio, the sample and device levels. The total extraction from the polar solvent and the extraction from one of the non-polar solvents that yields the higher amounts of extractables should be used for both quantitative and qualitative analyses. Extracts that may contain oligomeric or polymeric species should have the molecular weight distribution provided, along with the number and weight average molecular weights and the polydispersity. Experimental evidence should be provided to show that exhaustive extraction has been achieved with one of the solvents. The percent recovery, especially for the polydimethylsiloxanes (up to D20), should be reported.

All chemicals below a molecular weight of 1500 should be quantified and identified after exhaustive extraction of the final sterilized device. These include, but are not limited to, residual monomers, cyclics, and oligomers; known toxic residues such as polychlorinated biphenyls (PCBs) if dichlorobenzoyl peroxides are used; and aromatic amines if polyurethanes are used.

All experimental methodology (e.g., GPC, GLC/MS, GLC/AED, and FTIR[1]) and raw data (including instrument reports) should be provided along with all chromatograms, spectrograms, etc. The practical quantitative limit should be provided when the analyte of interest is not detected.[2]

1.2.3 Heavy Metals

Qualitative and quantitative analysis for heavy metals and residues of catalysts should be provided. The heavy metal analysis should include, but not be limited to, analysis for the following metals: platinum (Pt), tin (Sn), zinc (Zn), chromium (Cr), arsenic (As), lead (Pb), antimony (Sb), nickel (Ni), and copper (Cu). The valence status of the metals that were

[1] GPC = Gel Permeable Chromatography; GLC = Gas Liquid Chromatography; MS = Mass Spectometry; AED = Atomic Emission Detector; and FTIR = Fourier Transform Infrared Spectroscopy

[2] Keith, L. Compilation of EPA's Sampling and Analysis Methods. Lewis publishers, 1992.

used as catalysts in the curing reaction should be provided.

In lieu of providing a complete heavy metal analysis on the finished shell, a sponsor may choose to provide the purity of the catalyst (with trace elements) used in the raw shell material along with an analysis of the finished shell for just the catalyst metal used.

1.2.4 Other Chemical Data

The elastomer shell should be analyzed for volatile components. The elastomer should be cut into small pieces (2mm x 2mm), and headspace detector analyses should be performed.

Infrared spectroscopic analyses (FTIR) should be performed on both the cured polymer and extractable residuals.

Residues of ethylene oxide and ethylene chlorohydrin should be reported if ethylene oxide is used for sterilization.

Additives and adjuvants used in the manufacture of the device, such as plasticizers and antioxidants, should be reported.

Confirmation that the silica used in the dispersion is in the amorphous form, rather than crystalline form, should be provided.

1.3 Chemical Analysis of Filler Materials

1.3.1 Saline

Normal physiological sterile saline has a long history of use in breast implants and is standardized by the USP. As stated above, the sterile saline to be used with the implant should conform to USP standards of Normal Physiological Saline (injection grade) which has a concentration of 0.15M and a pH of 7.2-7.4. If the breast implant is to be used with any other saline, then a complete chemical analysis of the saline should be provided.

1.3.2 Silicone Gel

The requirements for the analysis of the gel are very similar to those for the elastomer shell. A detailed chemical analysis of the gel product should be provided, including both qualitative and quantitative analyses for volatiles, heavy metal contents, and extractables such as cyclic polysiloxanes. This information should include the identification of the polymers present, molecular weight averages and polydispersities of the polymers, and the identification and quantification of all compounds present with a molecular weight of 1500 or less.

1.3.3 Alternative Filler - Polymer

If the filler is a polymer material, the following information should be provided:

- the rationale for the use of the specific alternative material
- a list of all the components used in the synthesis and the method of synthesis of any polymer used in the preparation of filler (if it is a synthetic polymer) or the source and isolation procedure of the polymer, if it is a natural polymer
- the method of purification of the polymer
- the formulation of the polymer (the ratio of polymer should be specified if the filler material is a mixture of more than one component)
- the structural analyses of the polymer, including molecular weight distribution
- quantification and identification of all chemicals below a molecular weight of 1500, including the monomer and their characterization
- the trace metal/heavy metal analysis and the valence status if the metals were used at catalysts in the polymerization reaction
- the crosslink density (if it is a synthetic and cured material)

1.3.4 Alternative Filler – Non-Polymer

If the filler is a non-polymer material, the following information should be provided:

- the rationale for the use of the specific alternative material
- composition of the non-polymer, including characterization of smaller-molecular weight components
- the method of purification of the non-polymer
- the source and isolation procedure of the non-polymer
- the structural analyses of the non-polymer, including molecular weight distribution

2. Preclinical Data – Toxicology

2.1 General Information

The level of potential local and systemic toxicity of any substance introduced into the body by the breast implant should be assessed. Breast implants contain not only the major polymeric materials (e.g., polymerized polydimethylsiloxane), but also low molecular weight components, such as monomers, oligomers, catalysts, and residues from the sterilization process that can leach out into the patient's body.

The toxicological safety assessment is based on information from two sources, from the chemical composition of the device and from a standard battery of toxicological tests. Knowledge of the total levels of all polymers and residues or components of alternative materials in the final sterilized device provides an upper limit of the amounts of these chemicals that can be delivered locally to the implant site or into the systemic circulation. The identification and quantification of the chemicals present in the device (described in the chemistry section) may enable the usage of available information in the scientific literature about the toxicity and pharmacokinetics of these compounds. Chemicals without adequate safety data in the literature should be subjected to specific testing to obtain the required information. Individual compounds should be tested at least 10 times the local or systemic worst-case concentrations. In some cases, innovative delivery vehicles may be necessary to present chemicals to the toxicological test systems. The standard toxicological testing for the elastomer and the filler is described below in Sections 2.3 and 2.4.

The toxicity assessment should initially be based on the worst case levels of toxicants that would result if all the leachable compounds were released from the implant to the body at once. For some chemicals shown to be toxic at the worst-case concentration, it may be possible to demonstrate *in vivo* safety by demonstrating that the actual *in vivo* concentration levels of the compound will be considerably below the toxic level because of rapid rates of excretion and/or metabolism of the toxic compound.

2.2 Pharmacokinetic Studies

Knowledge of the pharmacokinetic behavior of potentially toxic chemicals is essential for the

scientific assessment of the potential human health risks resulting from the implant. Pharmacokinetics may be used to determine the rates of clearance of chemicals from the blood, the distribution in the body, and the routes and rates of metabolism and excretion of device-associated chemicals. The pharmacokinetic study designs chosen are determined by the information needed. When radiolabeling is used, the device should be radiolabeled in ways that will reflect the fates of all of the components of interest. Of toxicological concern are questions regarding the ultimate fate, quantities, sites/organs of deposition, and the rates and routes of excretion or deposition of potentially toxic compounds. For known toxic compounds, e.g., the low molecular weight cyclic siloxanes contained in silicone implants, the maximal serum concentration and tissue accumulation levels should be measured to determine if the compounds will produce significant adverse effects. These levels should be compared to the "no observed effect level" or "lowest observed effect level" determined from the literature or from studies using the isolated materials.

2.3 Biocompatibility Testing

A standard battery of toxicological tests is recommended in the ISO-10993 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing." This guidance suggests short-term and long-term biological tests that might be applied to evaluate the safety of implanted medical devices. Both the shell and the filler material should be tested separately. The recommended tests include cytotoxicity, short and intermediate-term implantation tests, acute systemic toxicity, hemocompatibility, immunotoxicity, reproductive toxicity, teratogenicity, genotoxicity, and carcinogenicity.

Additionally, the sponsor may refer to the guidance, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices - 5/1/95 - (G95-1)" which can be obtained at http://www.fda.gov/cdrh/g951.html. This guidance provides an overview of the general types of toxicity testing that should be considered for a medical device.

Section 2.4 below provides information to consider related to these tests.

2.4 Special Considerations

The level of immunotoxicity of the shell and any leachable compounds from the shell or the gel should be assessed. Sponsor should refer to the CDRH "Immunotoxicity Testing Guidance" for additional information; this guidance can be obtained at http://www.fda.gov/cdrh/ost/ostggp/immunotox.pdf.

Reproductive and teratogenicity studies should measure rates of conception as well as record the numbers of fetal deaths and malformations. The studies should include at least two generations. The dose of shell or filler material tested should be at least double the worst-case exposure level and higher, if possible. Individual compounds should be tested at the highest possible exposure that does not produce non-reproductive systemic toxicity.

Subchronic and chronic toxicity testing are essential because the leaching process may be slow, even when the material is in pulverized form, exposing the animals or cells to very small quantities of the leachable toxicants or carcinogens. Implanted material may also degrade over time, producing toxic degradation products. These cases can only be detected by subchronic or chronic implantation tests. The subchronic implantation test reports should include gross and histopathology examinations of the tissue surrounding the implanted material and at appropriate sites remote from the implantation

site.

Genotoxicity and carcinogenicity information is essential because the potential to cause cancer is an important concern for any implanted device. This potential may arise from leachable compounds and/or degradation products of the device. Therefore, adequate long-term studies with implantation of device materials should be conducted to evaluate the long-term toxic and carcinogenic potential. Complete reports from the genotoxicity testing of shell and filler from the finished sterilized device should be provided. The testing should, at minimum, consist of bacterial mutagenicity (including point and frame shift mutations) and a mammalian cell forward mutation assay. Mammalian cells should also be tested for cell transformation and for genetic damage in tests such as unscheduled DNA synthesis or chromosome aberration assays. Widely used, validated assays should be selected. Isolated compounds, mixtures, or extracts that are positive in any of the *in vitro* genetic toxicology tests should be tested in animals.

For silicone implants made using the current silicone chemistry, neither implantation tests nor clinical experience have, thus far, revealed carcinogenic effects. Therefore, FDA may consider approval of an IDE before the carcinogenicity tests are completed if the material(s) are similar and the *in vitro* genetic toxicology and clinical carcinogenic experience with the materials continues to be negative.

3. Preclinical Data - Mechanical

3.1 General Information

Breast implants are comprised of different designs. The basic components or design features of any breast implant are the shell, filler, and patch (or seal); optional components may include valves and/or adhesives. Preclinical testing is necessary to evaluate the material and mechanical properties of the specific breast implant under review.

Complete reports of the preclinical testing should include and/or address, at minimum, the following elements:

- testing conducted on finished, sterilized total devices or components (e.g., shell, gel, valve, etc.). This is imperative because the morphology and integrity of the materials and of the design features can be affected by processing. If the device is to be sterilized by different methods (e.g., ethylene oxide, gamma radiation, etc.), then preclinical testing should be performed on samples sterilized by the different methods unless an adequate rationale is provided that the change in sterilization method does not negatively impact the mechanical characteristics

- the implants tested including model and size, sample dimensions, etc.

- the rationale that the testing involved the worst case implant or representative models and/or sizes. When determining what is the worst case implant (or components of the implant), the sponsor should use implants (or components cut from that implant) manufactured with the thinnest shells allowed by the design release criteria

- the test set-up and methods including sketches or photographs of the set-up

- a statement whether the testing conditions (e.g., applied load, applied displacement, frequency, does testing continue on the remaining components, etc.) on the other implants are impacted if multiple samples are tested at one time

- the results with standard deviations, as well as the raw data and failure modes/analyses. As part of the results, a sponsor should prove that a statistically valid number of samples were used in each test performed

- an explanation of how or why the results are relevant if there are differences between the proposed and tested implants in terms of material, design, or sterilization method

- a discussion of the results in terms of the expected clinical performance

3.2 Tensile Strength and Ultimate Elongation

Tensile strength and ultimate elongation represent the largest sustainable stress and stretching deformation on a test specimen before rupture occurs, respectively. FDA suggests following the methodology described in ASTM D412 ("Vulcanized Rubber and Thermoplastic Rubbers and Thermoplastic Elastomers – Tension"). In terms of results, the sample thicknesses, tensile strengths, breaking forces, and ultimate elongations should be reported.

3.3 Tear Strength

Tear strength addresses the shell's resistance to propagation of a puncture or small tear. FDA suggests following the methodology described in ASTM D624 ("Tear Strength of Conventional Vulcanized Rubber and Thermoplastic Elastomers"). In terms of results, the sample thicknesses, tear forces, and tear strengths should be reported.

3.4 Integrity of Fused or Adhered Joints

Failure of a fused or adhered joint represents a potential source of leakage of the filler from the device. This testing provides a measure of the resistance of the device to such failures. Each joint (e.g., patch/shell joint, valve/shell joint) should be tested. FDA suggests following the methodology described in ASTM F703 which describes integrity of the joint after being subjected to 200% elongation after 10 seconds. However, in addition to that type of testing described in ASTM F703, destructive testing should be performed to determine the breaking force. In term of results for the first set of tests, the pass/fail results should be reported. In terms of results for the second set of tests, the breaking forces should be reported.

3.5 Valve Competence

This testing pertains only to implants with valves. Valve competence tests are performed to demonstrate that valve integrity is maintained at *in vivo* loads. Implants can be subjected to hydrostatic forces that tend to force fluid out of the device, causing a deflation and change in size and shape. The most likely source for increased pressure inside the devices would be from patients reclining with various body elements (head, arm, trunk, etc.) pressing on their implants.

ASTM F703 states that there shall be no leakage observable for five minutes after a normally closed

valve is subjected to a retrograde pressure equivalent to 30cm H_2O and then to a retrograde pressure equivalent to 3cm H_2O. FDA suggests following the methodology described in ASTM F703. However, FDA does not believe that the ASTM F703 methodology tests the efficacy of the device under actual *in vivo* load conditions. Therefore, the sponsor should predefine a pressure that adequately defines *in vivo* conditions, with a rationale, and provide testing at that pressure and perform visual inspection for leaking. In addition to that testing, destructive testing should be performed by gradually loading the specimens until valve failure occurs and a maximum pressure can be defined for the device. Whether the failed test valves reseal upon removal of the excess failure-inducing pressures should also be reported. In term of results for the first set of tests, the pass/fail results for leakage should be reported. In terms of results for the second set of tests, the burst pressures should be reported.

3.6 Cohesivity of Silicone Gel or Alternative Filler

This testing pertains only to silicone gel-filled and alternative filler implants. Cohesivity testing should be performed to measure both the rheological (flow) properties and the integrity (connectivity) of the gel. Two suggested methods are briefly described in ASTM F703. However, FDA does not believe that these ASTM methods were developed to address gels with high cohesivity. Therefore, while the methods may be appropriate for gels with low cohesivity, FDA believes that penetration-type testing can more accurately measure cohesivity in today's higher cohesive gels. For whatever method used to address cohesivity, the sponsor should provide a complete description of the test method used, including the pass-fail criteria, with an adequate rationale. The resulting values reported should be appropriate for the testing methodology.

3.7 Bleed Rates of Silicone Gel or Alternative Filler

Because gel or fluid can permeate or bleed through an intact shell, FDA believes that the bleed rate of a silicone gel-filled or of an alternative filler device should be determined. One possible method is described in ASTM F703. If this method is used, the normalized weight gain (weight of diffused silicone per contact surface area), the bleed rate (normalized weight gain per time interval), and the sample thicknesses should be provided.

3.8 Fatigue Rupture Testing of Total Device

Most materials have a finite fatigue life when repeatedly stressed or flexed. Repeated compression, folding, bending, or flexing of the device will, with time, weaken the material of the shell and eventually lead to shell failure. Therefore, fatigue compressive testing should be performed on the worst case, final, sterilized implant(s) in which a constant compressive load or constant displacement (often referred to as percent compression testing) is cyclically applied to an intact breast implant until it ruptures. However, constant displacement testing should only be performed if the sponsor can measure the actual applied loads continuously or at frequent points during the testing and the variation of the actual applied load is minimal. The minimal load applied during percent displacement testing should be used to establish the endurance load level.

The samples should be cyclically loaded to runout or failure at varying loads or displacements to generate an applied force versus number of cycles (AF/N) curve for the worst case implant(s). The runout value should be based on expected *in vivo* cycles subjected to the implant in its lifetime, and adequate rationale for the runout value should be provided.

FDA suggests that a sponsor test three samples at a given load or displacement from static point down to the endurance load level because of the general variance seen in elastomer testing. The sponsor should start with the static point and keep reducing the load or displacement for each subsequent test until a sample can reach runout (e.g., 6.5M cycles, 10M cycles) without failure. Whether load or displacement control testing is performed, a sponsor should provide AF/N curves. These curves may be generated by best-fit approach or by averaging the number of samples (e.g., 3) tested to establish a given point. There should be a tight range (e.g., 10%) of points around and at the endurance load level for a cleaner curve.

If a sponsor performs a load control fatigue test, then the sample thicknesses, applied loads, and the corresponding number of cycles to failure (unless it reached runout) should be provided. If a sponsor performs a displacement control fatigue test, then the sample thicknesses, applied displacements, applied loads, and corresponding number of cycles to failure (unless it reached runout) should be provided.

4. Preclinical Data - Other

4.1 Stability Data of Alternative Breast Implants

For a breast implant with an alternative filler, whether the filler is a polymer or non-polymer, long-term stability and accelerated aging studies (at least to 45°C) to demonstrate the effects of time and temperature on the physical properties and chemical composition of the device as a whole and of the filler material should be provided. Key physical parameters of the filler such as viscosity and cohesivity should be measured at each time point. If there are mechanical changes, complete chemical analyses should be conducted to explain the physical changes.

4.2 Bleed Material Analysis of Alternative Filler

FDA is concerned with the changes in composition of the alternative filler resulting from long-term chronic bleed, for which there is little known information. Because of the large number of possibilities of components for alternative filler materials, there is no existing test standard. The sponsor should provide a complete description of the testing methodology with a schematic of the setup and a rationale. The rationale for the set-up should be based on the specific chemical make-up of the alternative filler device. Sponsors are advised to submit a protocol to PRSB before initiating this testing.

4.3 Shelf Life

Both mechanical testing and package integrity testing are used to establish the expiration date for the labeling.

For mechanical testing, ultimate elongation, joint testing, and, if applicable, valve competency testing should be performed on representative aged samples.

For package integrity testing, a sponsor should address the information described in the guidance "Shelf Life of Medical Devices" and available on our website at http://www.fda.gov/cdrh/ode/415.pdf. To address package integrity the following testing should be considered and performed on representative samples under conditions of shipping, handling and storage: peel strength, bubble emission, dye penetration, visual inspection, and microbial challenge testing. Testing should be validated for the specific device packaging to assure there are adequate barrier properties to assure sterility under conditions of shipping, handling, and storage. To note, if dye penetration is to be used in lieu of microbial challenge testing, this should be validated to assure that package defects allowing contamination are easily detectable with this method.

CLINICAL DATA

5.1 General Information

FDA believes that a PMA may be filed with a minimum of 2 years of patient follow-up on a sufficient cohort of patients to evaluate the safety and effectiveness of the product. This is based on additional post-PMA filing follow-up for a total of a minimum of 10 years of prospective patient experience. Sample size estimates should be based on the precision of safety and effectiveness outcomes or based on detecting a clinically meaningful difference at 2 years from baseline or from a control group, but with consideration to lost-to follow-up rates estimated for 10 years of patient follow-up.

Safety and effectiveness and risk/benefit assessments must be based on valid scientific evidence as defined in 21 CFR 860.7(c)(2) from well-controlled studies as described in 21 CFR 860.7(f).

Studies should include the separate patient cohorts of primary augmentation, primary reconstruction, and revision. Because these studies are complicated by the fact that some patients receive implants for different reasons (e.g., a woman may receive one implant for reconstruction and one for augmentation) data should be recorded and analyzed on both a per patient and a per device basis. The patient/device is classified by indication at study *entry*. The following should be considered when classifying a

patient/device:

- If a reconstruction patient undergoes contralateral augmentation, that *patient* is classified as reconstruction. The device classification is one reconstruction and one augmentation.

- If a revision patient (i.e., the patient entered the study due to replacement of an existing implant, regardless of the type/manufacturer of the original implant), undergoes contralateral augmentation, that *patient* is classified as a revision patient. The device classification is one revision and one augmentation.

- If a revision (removal with replacement) occurs during the study (i.e., after initial implantation), the *patient/device* is classified based on the indication at original implantation at study entry.

If patients undergo removal and replacement with the same manufacturer's implant, then continued follow-up is expected. For patients who undergo removal without replacement or removal with replacement with another manufacturer's implant, FDA still encourages sponsors to continue follow-up evaluations**.**

Full patient accounting and adequate and appropriate safety and effectiveness data presentations are essential. **Please refer to Appendix I for general suggestions on the minimal type(s) of data and type(s) of data presentation for breast implants.**

5.2 Study Design / Statistical Issues

A complete description of the protocol should be provided. This includes explanations of the study objectives, descriptions of primary and ancillary hypotheses, definitions of the study population (i.e., inclusion and exclusion criteria), methods of randomization (if used), number and locations of investigational sites, enrollment procedures, descriptions of surgical techniques, and description of allowable ancillary surgical interventions and/or drugs. In addition, an explanation of how a control group was selected, if utilized for comparison, should be provided. Otherwise, an adequate justification for lack of use of a concurrent control group should be provided. Because saline-filled implants are currently approved, sponsors should consider utilizing this as a comparison group.

Confidence intervals around adverse event rates may be used for the safety profile. This includes the hypothesized rates of grade III/IV capsular contracture, removal for any reason (regardless of replacement), infection, and rupture. Any hypotheses to be tested, both null and alternative, should be clearly stated. Hypothesized rates of effectiveness benefits (i.e., improvement in body esteem scale) may also be included. Appropriate statistical techniques should be defined prospectively if employed to test hypotheses that support claims of safety and effectiveness.

Adequate demonstration that the patients in the study are representative of the population for whom the device is intended (i.e., with respect to patient age and indication for use) should be provided. This may be based on detailed patient demographic analyses and characterizations of patient baseline characteristics.

Statistical rationale that the sample size is adequate to provide accurate measures of the safety and effectiveness of the device should be provided. This includes, at a minimum, identification of effect criteria (clinically significant difference in the response variables to be detected), desired precision for rate estimates, statistical error tolerances of alpha and beta, anticipated variances of response variables (if known), any assumptions or statistical formulas with copies of references used, reasonable estimations of lost-to-follow-up rates, and all calculations used. Sample size estimates should be based on the precision of safety and effectiveness outcomes or detecting a clinically meaningful difference at two years from baseline or from a control group, but with consideration to lost-to follow-up rates estimated for 10 years of patient follow-up. If sample size estimates are based on the precision with which complication rates can be estimated, then the sample size should be large enough to ensure that this precision is within a pre-specified number of percentage points which FDA would consider acceptable, based on 95% confidence intervals. For example, for sufficient numbers of patients with primary augmentation or primary reconstruction (i.e., assuming 75% primary augmentation and 25% primary reconstruction) to determine the rupture rate with reasonable precision, 500 women will be needed to be followed at by the end of the study (i.e., 10 years post-implantation). Estimating a hypothetical 40% drop out rate at 10 years, enrollment of at least 850 patients will be needed. This will provide a worst case precision of +/-4% at a rupture rate of 50%, and this precision will improve as the rate moves away from 50%, with a +/-1.9% precision at a rupture rate of 5% or 95%. Sample size may also be justified based on survival analyses, using the method of Peto, which would result in a worst-case precision of +/-3%, given the same sample size and dropout rate.[3] Because both safety and effectiveness data from patients presenting for revision of an existing implant may be significantly different from that of primary implantation patients, a proportion of patients presenting for revision should be included. For example, estimating that approximately 20% of patients present for breast implants due to revision, the final sample size should be increased by 20%. Therefore, approximately 1,000 total patients would need to be enrolled to accommodate recruitment of approximately 150 revision patients.

Statistical rationale for pooling across the following confounding variables should be provided:

- patient age
- investigational site
- device type (i.e., single lumen vs. multi-lumen)
- device surface texture (i.e., smooth vs. textured)
- valve type (e.g., diaphragm vs. leaf), if applicable
- device placement (i.e., subglandular vs. retromuscular)
- surgeon experience and/or surgical technique
- surgical incision site (e.g., periareolar, inframmary fold, axillary, etc.)
- timing of reconstruction (i.e., immediate vs. delayed)

All relevant variables should be reported for each subpopulation of patients in order to evaluate the risk/benefit ratio. For each relevant subgroup, a sufficient number of patients should be followed for a sufficient length of time to adequately support all claims (explicit and implied) in any PMA submission. Patient subgroups include primary (i.e., initial) augmentation, primary reconstruction without prior tissue

[3] Peto, Richard, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and Examples. British J. Cancer 35:1-39, 1977.

expander, primary reconstruction with prior tissue expander, and revision (either due to cosmetic, medical, or surgical reason(s) and following either initial augmentation or reconstruction).

Additional analyses for the degree of device safety and effectiveness are recommended for the following variables:

- patient age
- indication for use (i.e., augmentation vs. reconstruction vs. revision)
- etiology and duration of breast abnormality, if applicable
- device type (i.e., single vs. multi-lumen)
- device style
- valve type (e.g., leaf, diaphragm), if applicable
- device surface type (i.e., smooth vs. textured)
- surgical incision site (e.g., periareolar, inframammary fold, axillary, etc.)
- device placement (e.g., retromuscular, subglandular)
- investigational site
- surgeon experience and technique
- type of reconstruction (i.e., immediate vs. delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents (if used)
- incision size

Statistical analyses with logistic regression or Cox regression analysis is suggested to determine which of these variables are associated with each safety and/or effectiveness outcome.

To better understand variables associated with device rupture/deflation, Cox Proportional Hazards Regression on time to rupture/deflation should be used with certain adverse events as time-dependent covariates. The coefficient estimates would be relative risks (hazard ratios) of rupture/deflation based on transition to an adverse event. An advantage of this approach is that the rupture/deflation is quite clearly defined, and multiple adverse events can be easily handled as separate time-dependent covariates for each type of event. This also addresses the problem of competing risks.

Subgroup analyses are also suggested, at minimum, for the complications of capsular contracture III/IV, implant removal (regardless of replacement), infection, and leakage/deflation, and for the variables of surface texture, implant placement, surgical approach, and valve type (if applicable).

5.3 Safety Assessment

The following local complications have been determined to be crucial in determining the risks of breast implants.[4] Rates and time course evaluations for the following should be provided, regardless of the device relatedness of the event. For the time course presentations, survival analyses are recommended.

a. the incidence, timing, severity, and reason(s) for all implant removals (for either cosmetic, medical, or surgical reasons), for removal with replacement, and for removal without replacement

b. the frequency, reason(s), and severity of additional surgical procedures, (including but not limited to incision and/or drainage of abscess/hematoma/seroma, excision of masses/tissues/calcifications, capsulotomy - both open and closed - capsulectomy, etc.)

c. the incidence, reason(s), and consequences of device failures (including rupture, leakage, extensive silicone gel bleed or alternative filler material bleed)

d. the incidence, reason(s), severity, duration of, and the method of resolution of all other complications (including but not limited to Baker Grade of fibrous capsular contracture, infection, calcification, migration, extrusion, skin erosion, necrosis, lymphadenopathy, delayed wound healing, breast/chest/axillary mass(es) formation, iatrogenic injury, hematoma, pain, and seroma)

e. the incidence, severity, and consequences of cosmetic complications (e.g., distortion, wrinkling, scar formation, visibility of the implant, asymmetry)

f. the incidence, timing of, and severity of alterations in nipple or breast sensation

g. the incidence, timing of, and severity of interference and/or difficulties with lactation

h. the incidence and nature of difficulties with pregnancy

i. the incidence and nature of mammographic detection difficulties

j. the incidence and nature of mammographic changes

k. the incidence and cause of patient deaths (i.e., from post-mortem examinations)

l. the incidence and reason(s) of patient dissatisfaction due to implant complications and removal(s)

m. any other device malfunction or adverse health event (including any effects on the immune system--see next item--and the reproductive system)

For silicone gel-filled implants, the characterization of the time course evaluations, incidence, and clinical consequences of silent rupture should be provided. Silent rupture is defined as a loss in the integrity of the shell, regardless of whether or not the silicone gel material has been demonstrated to have migrated from the shell. The incidence, timing, and clinical consequences should be determined via prospective, sequential screening of a subgroup of the study population utilizing diagnostic radiographic or other

[4] Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. {IOM Report}

techniques of adequate sensitivity and specificity. For standard silicone gel-filled implants, magnetic resonance imaging (MRI) is recommended as the current method of choice for detecting this event. MRI of the breast should be performed with a dedicated breast coil and preferably in those centers experienced in performing and interpreting this type of examination.

Breast implants are known to alter the appearance and quality of radiographs produced by conventional mammography. For an individual patient undergoing screening mammography, the sponsor should collect the incidence and extent of tissue fibrosis and calcification around the prosthesis and their impact on the correct and timely detection of breast tumors by mammography.

Despite the large body of information published regarding breast implants and the development of rheumatic or connective tissue diseases (CTD), the association between breast implants and CTD remains unresolved. While recent, large studies[5,6,7] have provided some evidence that breast implants are not associated with a large increase (i.e., relative risk greater than 2) in defined CTD, these data are limited in that they are not prospective (resulting in potential underreporting due to recall bias), do not address incomplete symptomatology for definitive diagnosis, lack consistent evaluations and follow-up, lack adequate duration of follow-up, and report pooled data from a variety of implant compositions rather than from product specific compositions. Furthermore, in general, the population for which breast implants is indicated, particularly the augmentation cohort (i.e., females in the reproductive age group), is inherently at greater risk for developing CTD than the older population. Therefore, the sponsor should collect CTD data in a prospective manner for a sufficient duration of follow-up. More specifically, the sponsor should characterize the incidence and time course presentations for the development of:

- rheumatic diseases - including but not limited to rheumatoid arthritis, systemic lupus erythematosus, discoid lupus, scleroderma, vasculitis, polymyositis, dermatomyositis

- rheumatic syndromes - including Raynaud's phenomenon, Sjogren's syndrome, CREST, morphea, carpal tunnel syndrome, multiple sclerosis-like syndrome, multiple myeloma-like syndrome, chronic fatigue syndrome, and fibromyalgia

- rheumatic signs and symptoms - such as hair loss, facial rash, photosensitivity, dry eyes, dry mouth, arthralgias, myalgias, difficulty swallowing, morning stiffness >30 min, ocular inflammation/retinitis/optic neuritis, muscle weakness, joint swelling for >6 weeks, pleurisy, skin rash, and lymphadenopathy

- other reported signs/symptoms - such as cognitive dysfunction, fatigue, paresthesia, dizziness, abnormal bruising or bleeding, purpura, unexplained fever, urticaria, telangiectasia, and petechiae

This CTD evaluation should be conducted on all patients yearly, with follow-up by a rheumatologist or other appropriate specialist, if indicated, and with collection of serological information (e.g., ANA, RF, ESR, immunoglobulin levels, CPK, SPEP, complement levels, etc.) if indicated.

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[5]Hennekens CH, Lee IM, Cook NR, *et al*. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA*. 1996; 275:616-621.

[6]Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liange MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med*. 1995; 332:1666-1670.

[7]Gabriel SE, O'Fallon WM, Kurkland LT, Beard CM, Woods JE, Melton LJ III. Risk of connective-tissue diseases and other disorders after breast implantation. *N Eng J Med*. 1994; 330:1697-1702.

Patients should be monitored periodically and regularly for the occurrence of all complications and adverse events for a minimum of 10 years post-implantation (see Section 5.2 for a detailed description on sample size assessment). Follow-up frequencies are suggested as, at a minimum, of 3, 6, 12, 18, and 24 months, and then, at minimum, annually thereafter. Annual visits after the 2-year time point are recommended due to retention of postal address changes of one year and to minimizing lost-to-follow-up.

The purpose of these visits/contacts is to assess for the incidence, severity, duration of, and method of resolution of the following, at a minimum:

- pain
- masses
- rupture/leakage
- explantation with or without replacement for either cosmetic, medical, or surgical reasons
- grade III/IV capsular contracture
- presence and consequences of additional surgical procedures (including but not limited to capsulotomy -- both open and closed -- capsulectomy; incision and/or drainage of abscess, hematoma, seroma; and removal of masses, tissues, calcifications)
- cosmetic complications (i.e., wrinkling, distortion, visibility of the implant, and asymmetry)
- lactation difficulties
- pregnancy complications
- mammographic changes and/or difficulties
- radiographic assessment for silent rupture (gel-filled and possibly alternative-filled)
- active CTD follow-up

5.4 Effectiveness Assessment

All marketing claims (both explicit and implied) of equivalence or superiority to existing implants or therapies should be supported with statistically justified numbers of patients, clinically relevant endpoints, and with direct comparisons made to an appropriate control group.

The anatomical effect of the implant should be assessed. This may be evaluated by comparing matched analyses of before and after bra and cup sizes, symmetry, and/or other standardized measurements. The health related quality of life (HRQL) benefits should be evaluated using valid and reliable instruments to assess the beneficial impact of the device. To date, there are no HRQL instruments which have been developed and validated in a breast implant population which capture all of the important domains (i.e., physical, social, emotional) as well as the positive and negative aspects of implantation on breast implant recipients. In order to make claims of improvement in health related quality of life, sponsors should develop and validate such measures for their products in a breast implant population. However, at minimum, the following health outcome assessments should be included in breast implant studies as secondary endpoints of effectiveness: a measure of self esteem (i.e., Rosenberg Self Esteem scale), a measure of body image (i.e., Body Esteem Scale), and a measure of general health related quality of life (i.e., SF-36). These assessments should be prospectively collected for presurgical and postsurgical repeated measures. Sponsors should describe the timing of administration of these instruments with respect to delayed versus immediate reconstruction in reconstruction patients. Stratification of the data according to indication (i.e., augmentation, reconstruction, and revision) as well as correlation of these data with other clinical outcomes and other control/comparison groups is recommended. The minimum duration of these assessments should be sufficient to capture stabilization of these parameters. A minimum duration of 2 years is recommended.

It is recommended that a measure of global patient satisfaction be assessed. This assessment should incorporate the effects of the initial surgical procedure, any adjunctive surgical and medical procedures, any complications, and whether the expected benefits of the procedure and of the implants have been met. Patient satisfaction data assessing the effects of device explantation, regardless of whether the device was replaced, is suggested, as well.

5.5 Retrieval Study

Because of the major concern of the high or unpredictable rate of implant failure and the lack of understanding of the mode of failure, FDA believes that a properly structured retrieval study involving clinical data collection and post-explant analyses may be more useful at this time than pursuing fold flaw and abrasion testing from sponsors. However, depending on the results of the retrieval study or the development of an acceptable testing methodology for fold flaw and/or abrasion testing that allow for better correlation to in-vivo conditions, additional mechanical testing may be necessary.

The retrieval study involves two portions.

The first portion of the retrieval study involves the collection of data at the time of explantation. The data should be recorded on a field report form by the surgeon and/or appropriate healthcare provider at the explant site. The following data should be collected:

- the reason (i.e., signs and symptoms) for the explant
- any complications experienced and the method of resolution
- any action planned (e.g., replacement with another implant with identification of the manufacturer, type, and model of the new device)
- relevant clinical observations at surgical explantation (e.g., appearance of shell for gross defects; the condition of the valves and/or patches, etc.)
- whether concomitant capsulectomy is performed
- presence of discoloration of and quantification of extruded filler
- the presence and extent of implant rupture
- the condition and appearance of surrounding capsule and/or other tissues removed
- the mode of failure of the explant, if known
- the relevant histological examinations of surrounding tissue or cells

The second portion of the retrieval study protocol involves inspections and/or tests performed on the explanted devices received by the sponsor. This portion of the study should focus on determining the mode of failure, rather than determining general properties of the retrieved devices (e.g., tensile strength). At minimum, visual inspections should be performed on all explanted devices received. Additionally, chemical and/or physical testing may be necessary to determine the mode of failure/reason for explantation. For example, a sponsor may be able to tell immediately the reason for the explantation (e.g., deflation due to patch tear/rip); however, chemical and/or physical testing may be necessary to determine the actual mode of failure. The study plan should list all visual inspections that will be performed on all explanted devices received, and it should list all chemical and physical tests that may be performed on explanted devices, depending on the individual case. There should be a standardized method of sterilization for the explant sites in order to minimize the factors that may impact mechanical properties.

5.6 Special Considerations

Implant failure is a critical assessment. Therefore, sponsors should advise against closed capsulotomy because it has been shown to potentially result in implant rupture. Additionally, sponsors should advise against the addition of substances into the filler (i.e., betadine, steroids, and antibiotics) other than those recommended because the substance may potentiate and/or accelerate delamination of the shell.

The stage and status of breast cancer can impact on future development of cancer. Furthermore, the presence of chemotherapy, radiation, or other cancer treatments can impact the development of local complications with implants. These issues may impact the evaluation of the safety and effectiveness of the device. Therefore, these data should be collected on all reconstruction patients and on augmentation/reconstruction patients who develop breast cancer during the course of the study.

High lost-to-follow-up rates may impact the evaluation of the safety and effectiveness of the device. A comparison of baseline characteristic between those subjects with complete data and those without should be included in order to ascertain the presence of any non-respondent bias. Also, sponsors are encouraged to offer incentives for patient retention. Otherwise, sponsors should be prepared to contact lost-to-follow-up patients at the end of the study and to demonstrate that the outcomes for these patients are the same as those for the patients who were compliant with follow-up. Failure to do this may delay filing and/or approval of the PMA because additional clinical studies may be needed.

5.7 Special Considerations for Alternative Breast Implants

The minimum period of both premarket and total patient follow-up will be determined individually for each alternative breast implant based on chemical, toxicological, mechanical, and clinical properties of the implant. Sponsors should expect to provide at least 2 years of premarket data for PMA filing for any implant, with longer premarket follow-up needed depending on the properties of the implant.

Unless an adequate rationale is provided, silent rupture data for an alternative breast implant should be collected. The data should include time course evaluations, incidence, and clinical consequences of silent rupture by MRI or some other appropriate imaging method. Any rationale for not collecting silent rupture data on the alternative filler should be based on chemical and/or mechanical properties as compared to saline (rapid leak) and silicone gel (slow leak) fillers.

5.8 Postapproval Study Considerations

FDA expects that patients be evaluated for a minimum of 10 years, some of which is premarket and some of which is postmarket evaluation. Again, we believe that a minimum of 2 years of premarket data is necessary to support a PMA. The clinical sections above describe the type of premarket data that should be collected. After approval of a PMA, follow-up of patients out to 10 years should continue through a postapproval study protocol. The study design of the postapproval study should be based on the specifics of the data submitted in the PMA. However, the following type of data, at minimum, should be collected annually as part of a postapproval study:

- pain
- capsular contracture
- deflation/rupture
- silent rupture, if applicable
- reoperation/removal with reasons
- satisfaction

After approval of a PMA, the sponsor may also be required to develop a retrieval study to collect data on implants removed.

Additionally, the risks of cancer(s), connective tissue disorders, reproductive/teratogenic effects, interference of implant on ability of mammography to detect tumors in breast implants, interference with breast feeding, and the later effects on offspring from women with implants may not be fully evaluated through the prospective clinical study described above nor from the literature as discussed in Section 5.9. If there is insufficient evidence in the medical literature or from experimental animal data to make reasonable judgements on the effect of implant type (i.e., silicone gel-filled, saline-filled, alternative-filled, and/or alternative shell) on these outcomes, then FDA may require additional postapproval studies to address these outcomes, as well.

5.9 Supplemental Information

Certain outcomes may not be fully evaluated through the preclinical and clinical data above. These outcomes include the risks of cancer(s), connective tissue disorders (typical and atypical), reproductive/teratogenic effects, interference of implant on ability of mammography to detect tumors in breast implants, interference with breast feeding, and the later effects on offspring from women with implants. Therefore, the sponsor should provide a thorough search of current and past medical literature on breast implants to address the range of clinical experience with each of these outcomes as they relate to the specific type of implant (i.e., silicone gel-filled, saline-filled, alternative-filled, and/or alternative shell), as well as the criteria and method of selecting the literature. Copies of the literature references should be provided. The sponsor should also develop a table that summarizes the information (see example table below). The numerators and denominators should be provided along with the rates.

Outcomes	**Literature**	**Implant Type(s)**
Cancer(s)	#patients with outcome / total patients, rate (%) for article 1 #patients with outcome / total patients, rate (%) for article 2	Saline only Saline/silicone gel
Typical CTDs		
Atypical CTDs		
Reproductive Teratogenic Effects		
Etc.		

[1] citation for literature article #1
[2] citation for literature article #2
etc.

In addition to those outcomes identified above, FDA also believes that a thorough literature search should be performed for the safety outcomes reported in the prospective clinical study (e.g., rupture, capsular contracture III-IV, infection, etc.). Additionally, the criteria and method of selecting the literature should be provided. A table, such as that shown above, should be provided.

FDA recognizes that it may be difficult to provide literature information specific to the subject breast implant type. The literature may pool silicone gel-filled and saline-filled breast implant information together. The literature may be lacking any information specific to alternative-filled breast implants. However, a sponsor should make every attempt to collect information specific to the subject breast implant type. If this is not feasible, then pooled data (e.g., silicone gel and saline data) from the literature should be provided. If this is not available, then data on the other type(s) of breast implant should be provided. For example, if no literature data exists for alternative-filled implants similar to that under review, then the literature summary should be provided for silicone gel and saline-filled implants.

Additionally, for alternative breast implants in which the alternative material(s) is utilized in another type of medical device, literature summarizing the clinical experience with the material should be provided.

LABELING

6.1 General Information

General labeling requirements for medical devices are described in 21 CFR 801. Additional labeling information may be obtained from the guidance, "Medical Device Labeling -- Suggested Format and Content" which is available at http://www.fda.gov/cdrh/ode/labeling.html. Additional sources of IDE labeling information may be found in 21 CFR 812.5, 812.7, and 812.20(b)(10), and PMA labeling information may be found in 21 CFR 814.20(b)(10). Both the IDE and PMA regulations require that copies of all labeling be provided.

Although the content within a piece of labeling may change from that provided in an IDE as compared to that provided in a PMA, package labels, a manufacturer's device card/sticker, a package insert, and patient information, at minimum, should be provided for any IDE or PMA.

A sponsor should refer to the FDA breast implant consumer handbook entitled, "Breast Implants – An Information Update – 2000" for potential risk information to consider when developing labeling. This handbook as well as additional information, such as patient labeling for Mentor and McGhan's saline-filled breast implants is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

Additionally, when developing the patient labeling, the sponsor should refer to "Guidance on Medical Device Patient Labeling" which is available at http://www.fda.gov/cdrh/ohip/guidance/1128.html and our information regarding plain language at http://www.plainlanguage.gov.

6.2 Package Labels

The outer package label(s) should include, at minimum, the following information:

- device name, style, etc.
- name and address of business of manufacturer, packer, or distributor
- quantity
- material
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date

If the breast implant is being studied under an IDE study, then the package label(s) must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

6.3 Manufacturer's Device Card/Sticker

This card/sticker is intended to be completed by the physician/surgeon and then given to the patient. This card/sticker should include, at minimum, the brand of the implant, its size, and the manufacturer's serial or lot number that a patient received.

6.4 Package Insert

The package insert for a breast implant is typically a combination package insert / surgical technique manual. However, the sponsor may choose to provide this information in separate pieces of labeling. Otherwise, the collective piece of information should include, but is not limited to, the following:

- device name, style, etc.
- name and address of business of manufacturer, packer, or distributor
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date
- brief device description with material information
- indications for use
- any relevant contraindications (including surgical procedures which are contraindicated due to interference with implant integrity and/or performance), warnings, and precautions
- list of potential adverse events
- procedures such as descriptions how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and troubleshooting procedures
- instructions for implantation, including surgical approach and device specific information (depends on type of breast implant)
- intraoperative test procedures to ensure implant integrity and proper placement (if necessary)
- instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period and during any subsequent surgical procedures, post-operative patient care, etc.
- how to evaluate, and how often to evaluate, implant integrity and placement

If the breast implant is being studied under an IDE study, then the package insert must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

If a PMA package insert is involved rather than one for an IDE study, then appropriate study safety and effectiveness results are to be included in addition to the items above.

The package insert should be made available to the patient after the surgery.

6.5 Patient Information

Patient information may be in the form of an informed consent document for an IDE study or in the form of what is generically referred to as patient labeling for an approved breast implant. However, this is not to say that a sponsor cannot provide additional patient labeling for an IDE study other than the required informed consent document. Note that the FDA informed consent document required for a patient to participate in an IDE study should not be confused with a standard consent form that a hospital requires to be signed by any patient. Patient information should not exceed the seventh grade reading comprehension level so that it is easily read and understood by most patients. Technical terms should be kept to a minimum and should be defined if they should be used. It should also be provided to patients at the initial visit/consultation so that each patient has sufficient time to review the information and discuss any issues with her physician(s).

The FDA informed consent document describes the purpose of the clinical study, the potential risks, etc. The specific elements, at minimum, required in an informed consent document are described in 21 CFR

50.25. The informed consent document should also include any other appropriate elements identified for the patient labeling below.

Patient labeling established for PMA-approved breast implants or as supplemental patient information for an IDE study should include the information needed to give prospective patients realistic expectations of the benefits and risks of device implantation. The patient labeling should include, at minimum, the following information:

- device name, style, etc.
- brief device description with material information
- indications for use
- relevant contraindications, warnings, and precautions
- potential complications, including the possible methods of resolution
- anticipated benefits and risks (to give patients realistic expectations of device performance)
- surgical alternatives, including no treatment or no implants and the benefits and risks of each
- postoperative care, including what to expect after surgery, symptoms to tell doctor about immediately, length of recovery, physical limitations, etc.
- factors to considers in the decision whether or not to get implants (may not be "lifetime" implant or one-time surgery, many of the changes to your breast following implantation are irreversible, breast implants may affect your ability to breast feed, routine screening mammography will be more difficult, health insurance coverage issues)
- other factors to consider (e.g., choosing a surgeon, implant size and shape, surface texturing, palpability, implant placement, incision sites)
- additional information related to the device such as lifetime replacement and reimbursement policy information, including estimated cost for replacement, costs not covered, etc.
- study safety and effectiveness results

Appendix I - Breast Implant Clinical Data Presentation

This appendix summarizes the types of data and data presentation suggested by FDA for reporting of safety and effectiveness clinical data for breast implants. This summarizes the minimal types of data presentation for a PMA submission and is not to be interpreted as being all-inclusive. Sponsors are encouraged to provide their own data presentations as well as those described below. While this encompasses all types of breast implants, some data presentations, such as silent rupture information, are applicable to silicone gel-filled or possibly to alternative implants and do not apply to saline-filled implants.

The majority of the data requested below should be reported for the **separate patient cohorts of primary augmentation, primary reconstruction, and revision** (i.e., the patient status/indication at study *entry*) as well as for the **total population**. See Section 5.1 above regarding specific patient cohort classification. Furthermore, the data should be provided on both a per patient and per device basis for most of the items below. Lastly, it is essential for the sponsor to provide all available data, including those data beyond the 2-year time point. The specifics are discussed within each item.

I. Patient Accounting

A. A full patient accounting table should be provided on both a per patient and per device basis for each **separate patient cohort** and the **total population**. See example Table 1 below. The deaths and explantations should be reported cumulatively (i.e., continue adding across the time points instead of just reporting the number specific to one time point). This information should include at least the following information:

1. theoretically due - number of patients/devices who would have been examined according to implant date and follow-up schedules;
2. deaths;
3. explantation without replacement;
4. explantation and replacement with different manufacturer's implant;
5. explantation and replacement with same manufacturer's implant;
6. expected – number of patients/devices theoretically due minus deaths and explantation without replacement and explantation and replacement with different manufacturer's implant;
7. actual number evaluated – number of complete patient/device follow-up examinations performed at each follow-up time point;
8. lost-to-follow-up – number expected minus actual number evaluated
9. % follow-up – actual number evaluated divided by expected

Example Table 1 showing cumulative patient accounting

	Periop	**1 year**	**2 years, etc.**
Theoretically Due	100	85	50
Deaths	0	1	1
Explantation w/o Replacement	0	2	2
Explantation & Replacement w/ Different Manufacturer's Implant	0	1	3
Explantation & Replacement w/ Same Manufacturer's Implant	0	4	6
Expected	100	81	44
Actual Number Evaluated	100	68	39

Lost-to-Follow-Up	0	13	5
% Follow-up	100/100 (100%)	68/81 (84%)	39/44 (89%)

B. Provide the causes for patients lost to follow-up, as well as any measures to be taken to minimize such future events.

C. Provide the causes for patient and physician-initiated discontinuations.

D. Provide the cause of any deaths, as well as the reports from post-mortem examinations.

It is our expectation that a minimum of 80% follow-up at the 2-year time point be provided at the time of PMA filing.

II. Safety

A. Report the **cumulative incidence** of complications at each scheduled visit on both a per patient and per device basis for each **separate patient cohort** and the **total population**. Provide this for both individual types of complications as well as for total (overall) complications.

1. If the same complication is reported in the same patient/breast more than once, it is counted once in the numerator if that same complication never resolved during the entire follow-up period. If a complication occurs in a breast/patient, resolves, and then recurs at a subsequent time point in the same breast/patient, it is counted twice in the numerator.

2. If >1 different or new complication occurs in the same patient/breast cumulatively, it is counted more than once in the numerator and once in the denominator for per patient and per device reporting for the total (overall) data presentation. Note that each capsular contracture grade is considered a new or different complication.

3. Provide the numerator and denominator used, and describe how these values were obtained. The denominator is the number of patients/devices at that visit.

B. Perform Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on both a per patient and per device basis for each **separate patient cohort** and for the **total population** for every complication, including the endpoints listed below. To avoid the problem of competing risks, a patient experiencing a complication should be a candidate to experience any other potential complication.

1. Rupture/deflation
2. Capsular contracture grades II, III, and IV separately
3. Capsular contracture grades II and higher
4. Capsular contracture grades III and higher
5. Explantation (removal) for any reason regardless of replacement
6. Explantation (removal) for any reason with replacement
7. Explantation (removal) for any reason without replacement
8. Infection
9. Any surgery/procedure/reoperation (i.e., even drainage of hematoma or abscess) to the breast or surrounding area. For example, excision of masses/lymph nodes in the ipsilateral

axilla or arm of an implanted breast can be considered the surrounding area

10. Any surgery/procedure/reoperation due to complication
11. Occurrence of any (≥1) complication

C. Report the total number of adverse events on both a per patient and per device basis for each **separate patient cohort** and for the **total population** at each follow-up visit.

1. Provide the total number of events categorized as mild, moderate, severe, etc. (if available).

2. If the same event occurred more than once in the same patient/breast, count it more than once.

D. Report the cumulative reasons for implant removal for each **separate patient cohort** and for the **total population** at each follow-up visit on a per device basis.

1. The denominator should be the total number of devices removed since the initial implantation.

2. If more than one reason is reported for removal, then assign one reason based on the following hierarchy: rupture/deflation, contracture, infection, necrosis/extrusion, hematoma/seroma, pain, wrinkling/asymmetry/scarring/malposition, and patient request for style/size change.

E. Report the Kaplan-Meier analysis (i.e., 1 minus the complication-free survival rate over time) on a per device basis for each **separate patient cohort** and for the **total population** for every complication occurring after implant removal with replacement as in II.B. above. Use the date of implant replacement as the beginning time point for this analysis.

General notes for reporting of complications:

- Include a new (after implantation) diagnosis of breast cancer as a complication in the above analyses.
- Explantation (removal) for any reason (cosmetic included), with or without revision, should be included as a complication and reported in the above analyses.
- Revision (explantation with replacement) for any reason (including cosmetic, such as change in size) should be included as a complication and reported in the above analyses.
- Note that each capsular contracture grade is considered a new or different complication.

III. Covariate Analyses

A. Perform logistic regression analyses, where appropriate, for safety endpoints on a per device basis for each **separate patient cohort** and for the **total population** using the covariates below. At a minimum, this should include the safety endpoints listed above in II.B (Kaplan-Meier complications).

1. Placement (i.e., subglandular or retromuscular)
2. Smooth vs. textured implant
3. Valve type (e.g., leaf, diaphragm, etc.)
4. Incision site (e.g., periareolar, inframmary, etc.)
5. Incision size

B. Perform Cox regression analyses for the adverse event of rupture/deflation on a per patient basis for each **separate patient cohort** and for the **total population** using static covariates (e.g., A.1-5 above), as well as time-dependent covariates (e.g., infection, capsular contracture, etc.).

IV. Effectiveness

A. Size

1. Report the frequency distribution of bra cup size at baseline, end of study, and change from baseline. Report results on both a per patient and per device basis for each **separate patient cohort** and the **total population.**

2. Report mean, median, mode (± SD) values of chest/bust circumference/measurement at baseline, end of study, and change. Report results on both a per patient and per device basis for each **separate patient cohort** and the **total population.**

3. For the augmentation cohort, report a matched two-way table of the number of patients in each cell demonstrating a change in bra cup size from before to after (e.g., the before-values on the y-axis and after on the x-axis with each cell representing the number of patients with a change from each before to after).

B. Body/Self-Esteem

1. Report the mean (± SD) change in each validated measure (pre-op to each visit). Report results on a per patient basis for each **separate patient cohort** and the **total population.**
2. The denominator is the number of patients at each visit.

3. Report results stratified by device placement (i.e., submuscular versus subglandular).

4. For reconstruction patients, report results for immediate versus delayed reconstruction separately for the entire reconstruction cohort.

V. Connective Tissue Disease (CTD) Reporting

A. CTD Diagnosis - For each of the points below, provide the data on a per patient basis for each **separate patient cohort** and the **total population.** The denominator is the number of patients at that visit. CTD diagnoses include those listed as "rheumatic diseases" or "rheumatic syndromes" in Section 5.3 of this guidance.

1. Perform Kaplan-Meier analyses (i.e., the Systemic Lupus Erythematosus-free survival rate over time) on a per patient basis for each CTD diagnosis separately and for having one or more CTD diagnosis.

2. Report the cumulative incidence of CTD diagnoses on a per patient basis at each timepoint for each CTD diagnosis separately and for having one or more CTD diagnosis.

B. CTD Signs/Symptom Categories - For each of the bolded anatomical areas (symptom categories) below, provide the data on a per patient basis for each **separate patient cohort** and the **total population.** The denominator is the number of patients at that visit. A symptom category is defined as an anatomical or body function area (i.e., Skin, Muscle, Joint, Neurological, Gastrointestinal, and General). For example, the category of **Skin** includes alopecia, facial rash, pruritis, echymoses, etc. The category of **Muscle** includes myalgias, muscle weakness, and elevated CPK. The category of **Joint** includes arthralgia, arthritis, and morning stiffness. The category of **Neurological** includes cognitive dysfunction, memory problems, and multiple sclerosis-like symptoms. The **General** category includes fatigue, generalized pain, and fever.

1. Perform Kaplan-Meier analyses (i.e., the CTD symptom category-free survival rate over time) on a per patient basis for each symptom category separately and for having one or more positive symptom category. (A positive symptom category is defined as one or more symptoms reported in that category.)

2. Report the cumulative incidence of patients reporting at least one symptom per symptom category at each time point for each symptom category separately and for having one or more positive symptom category.

C. CTD Signs/Symptoms - For each rheumatic sign/symptom or other reported sign/symptom described in Section 5.3, report the results on a per patient basis for each **separate patient cohort** and the **total population**. The denominator is the number of patients at that visit.

1. Report the non-cumulative point prevalence of CTD signs/symptoms on a per patient basis at each time point for each CTD sign/symptom separately and for having one or more positive CTD sign/symptom.

2. Report the cumulative incidence of CTD signs/symptoms on a per patient basis for each CTD sign/symptom separately and for having one or more CTD sign/symptom.

VI. Silent Rupture Reporting

A. With regard to silent rupture reporting, analyses should be provided for each of the following **3 events**:

1. MRI diagnosis of rupture regardless of confirmation with explantation
2. Rupture noted at explantation regardless of MRI diagnosis
3. Rupture noted at explantation for explanted patients **or** MRI diagnosis of rupture without explantation

B. For each of the 3 events above, provide the following data analyses:

1. Provide Kaplan-Meier analyses over time on both a per patient and a per device basis for each **separate patient cohort** and the **total population**.

2. Report the cumulative incidence (i.e., number of new patients/devices at each time with the event) at each time point on both a per patient and per device basis for each **separate patient cohort** and the **total population**.

VII. Mammography Data Presentation

A. For patients who undergo screening mammography during the study, analyses should be provided for each of the following **3 events** separately:

1. Mammographic suspicion for tumor regardless of biopsy results
2. Mammographic suspicion for tumor with a biopsy positive for malignant tumor
3. Mammographic suspicion for tumor with a biopsy negative for malignant tumor

B. For each of the 3 events above, provide the following data analyses:

1. Report the non-cumulative point prevalence at each time point on both a per patient and per device basis for each **separate patient cohort** and the **total population**. The denominator is number of patients/devices at each time point.

2. Report the cumulative incidence (i.e., number of new patients/devices at each time with the event) at each time point on both a per patient and per device basis for each **separate patient cohort** and the **total population**.

3. Compare the data obtained in items B.1 and 2 above with that reported in the literature for aged-matched cohorts.